UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,103	09/09/2003	Daikichi Fukushima	Q77131	3399

7590 06/07/2006

SUGHRUE MION PLLC
200 Pennsylvania Avenue, NW
Washington, DC 20037-3213

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/657,103	FUKUSHIMA ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *3-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/700,397.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/9/03; 12/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Appendices A,B

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 09 September 2003 has been entered in full. Claims 1-6 are amended.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1, 2, and 10, drawn to an isolated polypeptide, classified in class 530, subclass 350.

   II. Claims 3-8, drawn to a cDNA molecule encoding the protein, classified in class 536, subclass 23.1.

   III. Claims 9 and 10, drawn to a monoclonal or polyclonal antibody, classified in class 530, subclass 387.1.

The inventions are distinct, each from the other because of the following reasons:

   a. Inventions I-III are directed to related products. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the protein of Group I can be prepared by processes which are materially different from recombinant DNA expression of Group II, such as by chemical synthesis, or by isolation and purification from natural sources. Additionally, the DNA of Group II can be used other than to make the protein of Group I, such in gene therapy or as a probe in nucleic acid hybridization assays. The protein of Group I can be used in materially different methods other than to make the antibody of Group III, such as in therapeutic or diagnostic methods (e.g., in screening). Finally, although the antibody of Group III can be used to obtain the DNA of Group II, it can also be used in materially different methods, such as in various diagnostic (e.g., as a probe in immunoassays or immunochromatography), or therapeutic methods. Furthermore, the distinct products require separate, distinct,

and non-coextensive searches. As such, it would be burdensome to search the inventions of Groups I-III together.

2. Because these inventions are independent or distinct for the reasons given above and the inventions require a different classification and field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

3. Restriction to one of the following inventions is also required under 35 U.S.C. 121:

Groups A-D. The inventions as they pertain to each of SEQ ID NOs: 3/4; 8, 11, and 14, classification dependent upon the nature of the inventions.

The inventions are distinct, each from the other because of the following reasons:

b. Inventions A-D are directed to related products. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, each of SEQ ID NOs: 3/4; 8, 11, and 14 is a unique amino acid sequence, requiring a unique search of the prior art. Searching all of the sequences in a single patent application would provide an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

3. During a telephone conversation with Drew Hissong on 23 May 2006 a provisional election was made without traverse to prosecute the inventions of Group I, claims 1, 2, 10 and Group A (SEQ ID NOs: 3, 4). Affirmation of this election must be made by applicant in replying to this Office action. Claims 3-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1, 2, and 10 and SEQ ID NOs: 3, 4 are under consideration in the instant application.

Specification

5. The abstract of the disclosure is objected to because it is not limited to a single paragraph. Correction is required. See MPEP § 608.01(b).

6. The disclosure is objected to because of the following informalities:

6a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a continuation of Application No. 09/700,397, filed November 14, 2000, now U.S. Patent No. 6,664,383..." should be entered.

6b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "AN ISOLATED OC001 POLYPEPTIDE".

Appropriate correction is required.

Claim Objections

7. Claims 1, 2, and 10 are objected to because of the following informalities:

7a. Regarding claims 1 and 2, the phrase "SEQ ID NOS." should be amended to recite "SEQ ID NOs:".

7b. Claim 10 recites a non-elected invention.

7c. Claim 10, line 2 is missing the word "a" after "with".

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 U.S.C. § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, and 10 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

The claims are directed to an isolated form of the polypeptide comprising the amino acid sequence shown in SEQ ID NOs: 3 and 4, homologue thereof, fragment thereof or homologue of the fragment. The claims also recite a polypeptide comprising the amino acid sequence of SEQ ID NOs: 3 and 4. The claims recite a pharmaceutical composition containing the polypeptide in association with pharmaceutically acceptable diluent and/or carrier.

The specification of the instant application teaches that the present inventors have isolated genes encoding proliferation and/or differentiation factors functioning in hematopoietic systems and immune systems (pg 3, 3rd paragraph). The specification also discloses that clone

OC001 is a full-length cDNA including a full cDNA sequence that encodes membrane proteins (OC001; SEQ ID NO: 3) (pg 4, 2nd full paragraph).

However, the instant specification does not teach any significance or functional characteristics of the OC001 polypeptide (SEQ ID NOs: 3, 4). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any activity. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with OC001. Without any information as to the specific properties of OC001, the mere identification of the polypeptide is not sufficient to impart any particular utility to the claimed polypeptides. Since significant further research would be required of the skilled artisan to determine how the claimed polynucleotide and polypeptide are involved in any activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative polypeptide (SEQ ID NOs: 3, 4):

1) to produce a variant polypeptide (pg 6)
2) to produce antibodies against the polypeptide (pg 7, 4th full paragraph)
3) to identify proteins that bind the polypeptide (pg 23, 2nd full paragraph)
4) to screen for agonists and antagonists (pg 23, 4th full paragraph)
5) to treat various diseases and disorders (pg 14-22)

Each of these shall be addressed in turn.

1) to produce a variant polypeptide. This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide. Further, the specification discloses nothing specific or substantial for the variant polypeptide that is produced by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) to produce antibodies against the polypeptide. This asserted utility is not specific or substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, therefore both polypeptide and its antibodies have no patentable utility. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) to identify proteins that bind the polypeptide. This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide. Additionally, the specification discloses nothing specific or substantial for the other proteins that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to screen for agonists and antagonists. This asserted utility is not specific or substantial. Such assays can be performed with any polypeptide. Nothing is disclosed about how a specific function of the polypeptide is affected by the compounds. Additionally, the specification discloses nothing specific or substantial for the agonists and antagonists screened. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) to treat various diseases and disorders. This asserted utility is not specific or substantial. The specification does not disclose which cells or tissues are to be targeted or which diseases or conditions are to be treated. The specification does not disclose if cells, tissues, diseases, or disorders are associated with altered levels or forms of the OC001 polypeptide. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

9. Claims 1, 2, and 10 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9a. However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 1, 2, and 10 would remain rejected under 35 U.S.C. § 112, first paragraph. Specifically, the specification teaches that a homologue of the polypeptide of SEQ ID NOs: 3 and 4 sill generally be at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the polypeptide comprising the said amino acid sequence over a region of at least 30, preferably at least 30, for instance 40, 60 or 100 more contiguous amino acids (pg 6, 2nd full paragraph). The specification also discloses that a fragment of the polypeptide comprising the amino acid sequence shown in SEQ ID NOs: 3 and 4 or its homologues will be at least 10, preferably at least 15, for example 20, 25, 30, 40, 50 or 60 amino acids in length (pg 6, 3rd full paragraph). It is noted that the Examiner has broadly interpreted the phrases "an isolated form", "the amino acid sequence *shown in* [emphasis

added] SEQ ID NO. 3 and 4", and "homologue thereof, fragment thereof or homologue of the fragment" as reading upon amino acid fragments of SEQ ID NOs: 3 and 4 and amino acid variants with any number of deletions, substitutions, or additions. However, the specification does not teach any variant, fragment, derivative, or homolog of the OC001 polypeptide other than the full-length amino acid sequences of SEQ ID NOs: 3 and 4. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, derivatives, and homologues recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an

active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

9b. The specification of the instant application also teaches a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 3 or 4, homolog thereof, fragment thereof, or homolog of the fragment (pg 24-25). However, the specification does not teach how to use an OC001 "pharmaceutical" composition without undue experimentation for the treatment of a disease or disorder in an animal. The specification lists diseases, disorders, and conditions to be treated (pg 14-22), but there are no working examples directed to a particular disorder in an animal or administration of the OC001 polypeptide comprising the amino acid sequence of SEQ ID NO: 3 or 4 to an animal for treatment. (Note, this issue could be overcome by deleting the word "pharmaceutical" from the claims.)

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity and to determine the proper dosage, route of administration, and duration of treatment of the OC001 polypeptide and to identify the appropriate patient population; the lack of direction/guidance presented in the

specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

10. Claims 1, 2, and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated form of the polypeptide comprising the amino acid sequence shown in SEQ ID NOs: 3 and 4, homologue thereof, fragment thereof or homologue of the fragment. The claims also recite a polypeptide comprising the amino acid sequence of SEQ ID NOs: 3 and 4. The claims recite a pharmaceutical composition containing the polypeptide in association with pharmaceutically acceptable diluent and/or carrier. It is noted that the Examiner has broadly interpreted the phrases "an isolated form", "the amino acid sequence *shown in* [emphasis added] SEQ ID NO. 3 and 4", and "homologue thereof, fragment thereof or homologue of the fragment" as reading upon amino acid fragments of SEQ ID NOs: 3 and 4 and amino acid variants with any number of deletions, substitutions, or additions. The claims do not require that the polypeptide possess any particular biological activity, nor any particular

conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is no identification of any particular portion of the polypeptide structure that must be conserved or any biological activity. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polypeptide species (SEQ ID NO: 3 or 4) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, derivatives, fragments, homologues, and homologues of the fragments of the amino acid sequence of SEQ ID NO: 3 or 4.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not

achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 3 or 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 2, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. The term "form" in claims 1, 2, and 10 is a relative term which renders the claims indefinite. The term "form" is not defined by the claims, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the term "form" is referring to. For example, is the term referring to a fraction or a gel containing the polypeptide? Or, is the term referring to the variants, fragments, and homologues of the polypeptide? (Please note that this issue could be overcome by amending claim 1, for example, to remove the phrase "form of the".)

13. Claim 10 is indefinite because the elements recited in the claim do not constitute proper Markush groups. The claim is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 2, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Struyk et al. (J Neurosci 15(3): 2141-2156, 1995). It is noted that the Examiner has broadly interpreted the phrases "an isolated form", "the amino acid sequence *shown in* [emphasis added] SEQ ID NO. 3 and 4", and "homologue thereof, fragment thereof or homologue of the fragment" as reading upon amino acid fragments of SEQ ID NOs: 3 and 4 and amino acid variants with any number of deletions, substitutions, or additions.

Struyk et al. teach an isolated polypeptide termed "neurotrimin" that is 90.8% identical to the claimed polypeptide of SEQ ID NO: 3 of the instant application (see Figure 3 of Struyk et al.;

see also sequence alignment attached to the instant Office Action as Appendix A). The neurotrimin polypeptide of Struyk et al. is also 98.4% identical to the claimed polypeptide of SEQ ID NO: 4 of the instant application (see sequence alignment attached to the instant Office Action as Appendix B). Struyk et al. teach a fusion protein corresponding to about two-thirds of the neurotrimin protein which is injected into rabbits (pg 2142, bottom of column 2 through the top of pg 2143).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
25 May 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER

Appendix A

```
RESULT 6
NTRI_RAT
ID   NTRI_RAT       STANDARD;      PRT;   344 AA.
AC   Q62718;
DT   01-NOV-1997, integrated into UniProtKB/Swiss-Prot.
DT   01-NOV-1996, sequence version 1.
DT   07-MAR-2006, entry version 43.
DE   Neurotrimin precursor (GP65).
GN   Name=Nt; Synonyms=Hnt;
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi;
OC   Muroidea; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 217-229.
RC   STRAIN=Sprague-Dawley;
RX   MEDLINE=95198094; PubMed=7891157;
RA   Struyk A.F., Canoll P.D., Wolfgang M.J., Rosen C.L., D'Eustachio P.,
RA   Salzer J.L.;
RT   "Cloning of neurotrimin defines a new subfamily of differentially
RT   expressed neural cell adhesion molecules.";
RL   J. Neurosci. 15:2141-2156(1995).
CC   -!- FUNCTION: Neural cell adhesion molecule.
CC   -!- SUBCELLULAR LOCATION: Cell membrane; lipid-anchor; GPI-anchor.
CC   -!- TISSUE SPECIFICITY: Central nervous system.
CC   -!- DEVELOPMENTAL STAGE: Expressed at high levels in several
CC       developing projection systems: in neurons of the thalamus,
CC       subplate, and lower cortical laminae in the forebrain and in the
CC       pontine nucleus, cerebellar granule cells, and Purkinje cells in
CC       the hindbrain.
CC   -!- SIMILARITY: Belongs to the immunoglobulin superfamily. IgLON
CC       family.
CC   -!- SIMILARITY: Contains 3 Ig-like C2-type (immunoglobulin-like)
CC       domains.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; U16845; AAA67445.1; -; mRNA.
DR   PIR; I56551; I56551.
DR   Ensembl; ENSRNOG00000023720; Rattus norvegicus.
DR   RGD; 620958; Hnt.
DR   InterPro; IPR013098; I-set.
DR   InterPro; IPR003599; Ig.
DR   InterPro; IPR007110; Ig-like.
DR   InterPro; IPR003598; Ig_c2.
DR   InterPro; IPR013151; Immunoglobulin.
DR   Pfam; PF07679; I-set; 1.
DR   Pfam; PF00047; ig; 2.
DR   SMART; SM00409; IG; 3.
DR   SMART; SM00408; IGc2; 2.
DR   PROSITE; PS50835; IG_LIKE; 3.
KW   Cell adhesion; Direct protein sequencing; Glycoprotein; GPI-anchor;
KW   Immunoglobulin domain; Lipoprotein; Membrane; Repeat; Signal.
FT   SIGNAL        1     33       Potential.
FT   CHAIN        34    321       Neurotrimin.
FT                               /FTId=PRO_0000015114.
FT   PROPEP      322    344       Removed in mature form (Potential).
FT                               /FTId=PRO_0000015115.
FT   DOMAIN       39    126       Ig-like C2-type 1.
FT   DOMAIN      136    218       Ig-like C2-type 2.
FT   DOMAIN      222    309       Ig-like C2-type 3.
FT   LIPID       321    321       GPI-anchor amidated asparagine
FT                               (Potential).
FT   CARBOHYD     44     44       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD     70     70       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    152    152       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    216    216       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    284    284       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    292    292       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    305    305       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    321    321       N-linked (GlcNAc. . .) (Potential).
FT   DISULFID     57    115       Potential.
FT   DISULFID    157    201       Potential.
FT   DISULFID    243    295       Potential.
SQ   SEQUENCE   344 AA;  37998 MW;  CBB39BE53B33B224 CRC64;

  Query Match             90.8%;  Score 1639.5;  DB 1;  Length 344;
  Best Local Similarity   92.9%;  Pred. No. 1.4e-127;
  Matches  312;  Conservative    9;  Mismatches   12;  Indels    3;  Gaps    1;
```

Appendix A (cont.)

```
Qy         12 ISWAIFTGLAALCLF---QGVPVRSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAW 68
              : |     ::   ||    ||||||||||||||||||||||||||||||||||||||||
Db          9 LPWKCLVVVSLRLLFLVPTGVPVRSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAW 68

Qy         69 LNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRV 128
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         69 LNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRV 128

Qy        129 HLIVQVSPKIVEISSDISINEGNNISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEI 188
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        129 HLIVQVSPKIVEISSDISINEGNNISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEI 188

Qy        189 QGITREQSGDYECSASNDVAAPVVRRVKVTVNYPPYISEAKGTGVPVGQKGTLQCEASAV 248
              |||||||||:|||||||||||||||| ||||||||||||||||||||||||||||||||
Db        189 QGITREQSGEYECSASNDVAAPVVRRVNVTVNYPPYISEAKGTGVPVGQKGTLQCEASAV 248

Qy        249 PSAEFQWYKDDKRLIEGKKGVKVENRPFLSKLIFFNVSEHDYGNYTCVASNKLGHTNASI 308
              |||||||:||||||:|||||||||||||||:| ||||||||||||||||||||||||||
Db        249 PSAEFQWFKDDKRLVEGKKGVKVENRPFLSRLTFFNVSEHDYGNYTCVASNKLGHTNASI 308

Qy        309 MLFGPGAVSEVSNGTSRRAGCVWLLPLLVLHLLLKF 344
              ||||||||||:|||||||||:|||||||||||||||
Db        309 MLFGPGAVSEVNNGTSRRAGCIWLLPLLVLHLLLKF 344
```

Appendix B

```
RESULT 6
NTRI_RAT
ID   NTRI_RAT       STANDARD;      PRT;   344 AA.
AC   Q62718;
DT   01-NOV-1997, integrated into UniProtKB/Swiss-Prot.
DT   01-NOV-1996, sequence version 1.
DT   07-MAR-2006, entry version 43.
DE   Neurotrimin precursor (GP65).
GN   Name=Nt; Synonyms=Hnt;
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi;
OC   Muroidea; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 217-229.
RC   STRAIN=Sprague-Dawley;
RX   MEDLINE=95198094; PubMed=7891157;
RA   Struyk A.F., Canoll P.D., Wolfgang M.J., Rosen C.L., D'Eustachio P.,
RA   Salzer J.L.;
RT   "Cloning of neurotrimin defines a new subfamily of differentially
RT   expressed neural cell adhesion molecules.";
RL   J. Neurosci. 15:2141-2156(1995).
CC   -!- FUNCTION: Neural cell adhesion molecule.
CC   -!- SUBCELLULAR LOCATION: Cell membrane; lipid-anchor; GPI-anchor.
CC   -!- TISSUE SPECIFICITY: Central nervous system.
CC   -!- DEVELOPMENTAL STAGE: Expressed at high levels in several
CC       developing projection systems: in neurons of the thalamus,
CC       subplate, and lower cortical laminae in the forebrain and in the
CC       pontine nucleus, cerebellar granule cells, and Purkinje cells in
CC       the hindbrain.
CC   -!- SIMILARITY: Belongs to the immunoglobulin superfamily. IgLON
CC       family.
CC   -!- SIMILARITY: Contains 3 Ig-like C2-type (immunoglobulin-like)
CC       domains.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; U16845; AAA67445.1; -; mRNA.
DR   PIR; I56551; I56551.
DR   Ensembl; ENSRNOG00000023720; Rattus norvegicus.
DR   RGD; 620958; Hnt.
DR   InterPro; IPR013098; I-set.
DR   InterPro; IPR003599; Ig.
DR   InterPro; IPR007110; Ig-like.
DR   InterPro; IPR003598; Ig_c2.
DR   InterPro; IPR013151; Immunoglobulin.
DR   Pfam; PF07679; I-set; 1.
DR   Pfam; PF00047; ig; 2.
DR   SMART; SM00409; IG; 3.
DR   SMART; SM00408; IGc2; 2.
DR   PROSITE; PS50835; IG_LIKE; 3.
KW   Cell adhesion; Direct protein sequencing; Glycoprotein; GPI-anchor;
KW   Immunoglobulin domain; Lipoprotein; Membrane; Repeat; Signal.
FT   SIGNAL        1     33       Potential.
FT   CHAIN        34    321       Neurotrimin.
FT                               /FTId=PRO_0000015114.
FT   PROPEP      322    344       Removed in mature form (Potential).
FT                               /FTId=PRO_0000015115.
FT   DOMAIN       39    126       Ig-like C2-type 1.
FT   DOMAIN      136    218       Ig-like C2-type 2.
FT   DOMAIN      222    309       Ig-like C2-type 3.
FT   LIPID       321    321       GPI-anchor amidated asparagine
FT                               (Potential).
FT   CARBOHYD     44     44       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD     70     70       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    152    152       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    216    216       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    284    284       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    292    292       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    305    305       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    321    321       N-linked (GlcNAc. . .) (Potential).
FT   DISULFID     57    115       Potential.
FT   DISULFID    157    201       Potential.
FT   DISULFID    243    295       Potential.
SQ   SEQUENCE   344 AA;  37998 MW;  CBB39BE53B33B224 CRC64;

  Query Match             98.4%;  Score 1616;  DB 1;  Length 344;
  Best Local Similarity   97.4%;  Pred. No. 5.6e-127;
  Matches  305;  Conservative    6;  Mismatches    2;  Indels    0;  Gaps    0;
```

Appendix B (cont.)

```
Qy          1 RSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAWLNRSTILYAGNDKWCLDPRVVLL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         32 RSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAWLNRSTILYAGNDKWCLDPRVVLL 91

Qy         61 SNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRVHLIVQVSPKIVEISSDISINEGN 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         92 SNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRVHLIVQVSPKIVEISSDISINEGN 151

Qy        121 NISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEIQGITREQSGDYECSASNDVAAPV 180
              ||||||||||||||||||||||||||||||||||||||||||:||||||||||||||
Db        152 NISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEIQGITREQSGEYECSASNDVAAPV 211

Qy        181 VRRVKVTVNYPPYISEAKGTGVPVGQKGTLQCEASAVPSAEFQWYKDDKRLIEGKKGVKV 240
              |||| |||||||||||||||||||||||||||||||||||:|||||||:||||||||
Db        212 VRRVNVTVNYPPYISEAKGTGVPVGQKGTLQCEASAVPSAEFQWFKDDKRLVEGKKGVKV 271

Qy        241 ENRPFLSKLIFFNVSEHDYGNYTCVASNKLGHTNASIMLFGPGAVSEVSNGTSRRAGCVW 300
              |||||||:| ||||||||||||||||||||||||||||||||||:||||||||||:|
Db        272 ENRPFLSRLTFFNVSEHDYGNYTCVASNKLGHTNASIMLFGPGAVSEVNNGTSRRAGCIW 331

Qy        301 LLPLLVLHLLLKF 313
              |||||||||||||
Db        332 LLPLLVLHLLLKF 344
```